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## (54) GEL PREPARATION COMPOSITION AND GEL PREPARATION

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain a gel preparation composition which contains a hydrophilic copolymer of a specific structure, a polyhydric alcohol and a physiologically active substance and is prepared by crosslinking its hydrophilic copolymer, thus manifests excellent transdermal absorption.
SOLUTION: This composition contains (A) a hydrophilic copolymer comprising (i) 10-90wt.% of a monomer unit bearing a carboxyl group, preferably (meth) acrylic acid and (ii) 90-10wt.% of other copolymerizable monomers, (B) a polyhydric alcohol and (C) a pharmacologically active substance, preferably at least one selected from progesterone, estradiol, testosterone, pindolol, clonidine, lidocaine and nifedipine and the component A is crosslinked. This composition is laminated to give a gel preparation. The amount of the component B is preferably 50-500 pts.wt., more preferably 100-400 pts.wt. per 100 pts.wt. of the component A, while the component C is preferably 5-100 pts.wt., more preferably 20-70 pts.wt.

## CLAIMS

[Claim(s)]
[Claim 1]A gel preparation constituent characterized by making this hydrophilic copolymer construct a bridge including a hydrophilic copolymer, polyhydric alcohol, and a pharmacological activity substance which consist of 10 to 90 weight % of monomeric units which have a carboxyl group, and 90 to 10 weight % of other copolymerizable vinyl system monomeric units.
[Claim 2]The gel preparation constituent according to claim 1 whose monomer which has a carboxyl group is acrylic acid or methacrylic acid.
[Claim 3]The gel preparation constituent according to claim 1 or 2 which are one or more sorts of substances chosen from a group which a pharmacological activity substance becomes from progesterone, estradiol, testosterone, pindolol, clonidine, lidocaine, and nifedipine.
[Claim 4]Gel preparation laminating a layer which becomes a support base from Claim 1 and the gel preparation constituent according to claim 2 or 3.

[Translation done.]

* NOTICES *



1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

## DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]This invention relates to a gel preparation constituent and gel preparation. In more detail, this invention has much skin transmission quantity of a pharmacological activity substance, and relates to a new gel preparation constituent and gel preparation excellent in percutaneous absorption.
[0002]
[Description of the Prior Art]Percutaneous absorption type pharmaceutical preparation has many advantages, such as evasion of the primary metabolism in intestines and liver, mitigation of side effects, and continuation-izing of an operation, as compared with the medication by taking orally or injection. The pharmacological activity substance in contact with the skin enters in the skin, and it is supposed that epidermis, and a hair follicle and a sudoriferous gland are it among the courses further absorbed in a blood vessel. However, it is said that the usable area of a hair follicle and a sudoriferous gland route is about 0.1%, and although the contribution is high in the early stages of application, a contribution falls by temporality and it becomes the absorption courses with main epidermis. On the normal skin, the checking action to the cutaneous absorption is in a horny layer, in many pharmacological activity substances, the pharmacological activity substance concentration in blood obtained by percutaneous absorption cannot be given to an effective therapeutic range, but there is a problem that a curative effect is not acquired. It is the pharmaceutical preparation which distributed and dissolved the pharmacological activity substance into polymer, and the matrix type pharmaceutical preparation which is the conventional percutaneous absorption type pharmaceutical preparation cannot dissolve a pharmacological activity substance in high concentration, but its percutaneous absorption of a

pharmacological activity substance is bad. In order to improve the percutaneous absorption of a pharmacological activity substance, the closed dressing method (ODT) is used widely, but the result which should be satisfied in addition has not come to be obtained. For this reason, percutaneous absorption type pharmaceutical preparation with a large percutaneous absorption speed of a pharmacological activity substance is called for strongly.
[0003]
[Problem to be solved by the invention]This invention has much skin transmission quantity of the pharmacological activity substance in pharmaceutical preparation, and is made for the purpose of providing a gel preparation constituent and gel preparation excellent in percutaneous absorption.
[0004]
[Means for solving problem]As a result of repeating research wholeheartedly that above-mentioned SUBJECT should be solved, this invention persons The hydrophilic copolymer of specified structure, It finds out that the gel preparation which has the percutaneous absorption outstanding from the constituent over which the hydrophilic copolymer was made to construct a bridge is obtained including polyhydric alcohol and a pharmacological activity substance, and came to complete this invention based on this knowledge. Namely, the hydrophilic copolymer in which this invention consists of 10 to 90 weight % of monomeric units which have (1) carboxyl group, and 90 to 10 weight % of other copolymerizable vinyl system monomeric units, The gel preparation constituent characterized by making this hydrophilic copolymer construct a bridge including polyhydric alcohol and a pharmacological activity substance, (2) The gel preparation constituent given in ** (1) clause the given monomer which has a carboxyl group is acrylic acid or methacrylic acid, A pharmacological activity substance (3) Progesterone, estradiol, testosterone, The ** (1) clause or the gel preparation constituent given in ** (2) clause which is one or more sorts of substances chosen from the group which consists of pindolol, clonidine, lidocaine, and nifedipine, And the gel preparation laminating the layer which becomes (4) support bases from a ** (1) clause, a ** (2) clause, or a gel preparation constituent given in ** (3) clause is provided. As a desirable mode of this invention, the content of (5) polyhydric alcohol, The ** (1) clause which is 50 to 500 weight section per hydrophilic copolymer 100 weight section, ** (2) The loadings of a clause or a gel preparation constituent given in ** (3) clause, and (6) pharmacological activity substances, The ** (1) clause which is five to 100 weight section per hydrophilic copolymer 100 weight section, ** (2) The ** (1) clause which constructs a bridge with a clause, a ** (3) clause or a gel preparation constituent given in ** (5) clause, and the polyfunctional compound that generates bridge construction by a reaction with the carboxyl group which (7) hydrophilic copolymers have, ** (2) A clause, a ** (3) clause, a ** (5) clause, or a gel preparation constituent given in ** (6) clause, (8) The ** (1) clause which added the percutaneous absorption auxiliary agent, a ** (2) clause, a ** (3) clause, ** (5) The gel preparation laminating the layer which becomes a clause, a ** (6) clause or a gel preparation constituent given in ** (7) clause, and (9) support bases from a ** (5) clause, a ** (6) clause, a ** (7) clause, or a gel preparation constituent given in ** (8) clause can be mentioned.
[0005]
[Mode for carrying out the invention]As a monomer which has a carboxyl group used for this invention, acrylic acid (meta), maleic acid (anhydrous), fumaric acid, itaconic acid (anhydrous), etc. can be mentioned, for example. In these, especially the thing for which acrylic acid and methacrylic acid are used is preferred. In the hydrophilic copolymer used for this invention, the content of the monomeric unit which has a carboxyl group is 10 to 90 weight %, and is 15 to 70 weight % preferably. There is a possibility that adhesive properties [ as opposed to / that the content of the monomeric unit which has a carboxyl group is less than 10 weight % / time of polyhydric alcohol content / the skin ] may run short. When the content of the monomeric unit which has a carboxyl group exceeds 90 weight %, the solubility to polymer of a pharmacological activity substance becomes insufficient, and there are a fall of the absorbed amount of a pharmacological activity substance and a possibility that continuous percutaneous absorption may not be obtained. As the monomer which has a carboxyl group, and other copolymerizable vinyl system monomers, For example, methyl acrylate (meta), ethyl acrylate (meta), butyl acrylate (meta), (Meta) Acrylic acid octyl, acrylic acid (meta)-2-ethylhexyl, (Meta) Acrylic acid

dodecyl, acrylic acid (meta) hydroxyethyl, (Meta) Acrylic acid hydroxypropyl, acrylic acid (meta) hydroxybutyl, (Meta) Acrylic acid aminoethyl, acrylic acid (meta) aminopropyl, (Meta) Acrylic ester, such as acrylic acid aminobutyl (meta), Aromatic vinyl monomers, such as styrene, alpha-methylstyrene, and p-methylstyrene, Vinyl heterocyclic compounds, such as vinyl ether, such as vinylmethyl ether, vinylethyl ether, vinyl propyl ether, and vinylbutyl ether, vinyl pyrrolidone, and vinylimidazole, etc. can be mentioned. These vinyl system monomers can be used combining independent or two sorts or more. There is no restriction in particular in the manufacturing method of the hydrophilic copolymer used for this invention constituent, for example, a radical-solution-polymerization method can be used preferably. Preferably in [ specifically dissolve the monomer which has a carboxyl group, and other copolymerizable vinyl system monomers in a suitable organic solvent, and inactive gas replaces atmosphere, add a polymerization initiator, and ] the temperature of the range of 50-80 **, A hydrophilic copolymer solution can be obtained by making it polymerize for about 5 to 40 hours. As a polymerization initiator, azo compounds, such as organic peroxide, such as benzoyl peroxide and cumene hydroperoxide, or 2,2'-azobisisobutyronitrile, etc. can be used, for example.

[0006]The gel preparation constituent of this invention contains polyhydric alcohol. To the same intramolecular, polyhydric alcohol is hydroxyl a compound which it has two or more pieces, and as such a compound, For example, ethylene glycol, propylene glycol, a butylene glycol, Glycerin, trimethylolpropane, pentaerythritol, arabitol, Sorbitol, a polyethylene glycol, a polypropylene glycol, diglycerol, polyglycerin, dipentaerythritol, diethanolamine, triethanolamine, etc. can be mentioned. In this invention constituent, one sort can be independently used for these polyhydric alcohol, and can be used for it combining two or more sorts. In a gel preparation constituent, it is thought that its percutaneous absorption of a pharmacological activity substance improves in order that polyhydric alcohol may swell the hydrophilic copolymer which constructed the bridge and may increase the solubility of a pharmacological activity substance and activity. In this invention constituent, as for the loadings of polyhydric alcohol, it is preferred that it is 50 to 500 weight section per hydrophilic copolymer 100 weight section, and it is more preferred that it is 100 to 400 weight section. There is a possibility that sufficient percutaneous absorption may not be revealed in the loadings of polyhydric alcohol being less than 50 weight sections per hydrophilic copolymer 100 weight section. When the loadings of polyhydric alcohol exceed 500 weight sections per hydrophilic copolymer 100 weight section, there is a possibility that the mechanical strength of a base material may fall. A pharmacological activity substance is blended with the gel preparation constituent of this invention. There is no restriction in particular in the pharmacological activity substance to blend, and For example, progesterone, A local anesthetic like estradiol, a hormonal drug like testosterone, pindolol, an antihypertensive drug like clonidine, lidocaine, and prilocaine, a coronary vasodilator like nifedipine, etc. can be mentioned. In this invention constituent, as for the loadings of a pharmacological activity substance, it is preferred that it is five to 100 weight section per hydrophilic copolymer 100 weight section, and it is more preferred that it is 20 to 70 weight section. There is a possibility that sufficient percutaneous absorption may not be revealed in the loadings of a pharmacological activity substance being less than five weight sections per hydrophilic copolymer 100 weight section. When the loadings of a pharmacological activity substance exceed 100 weight sections per hydrophilic copolymer 100 weight section, there is a possibility that it may become difficult to consider it as a uniform constituent.

[0007]A hydrophilic copolymer is made to construct a bridge in the gel preparation constituent of this invention. There is no restriction in particular in the crosslinking method of a hydrophilic copolymer, for example, a bridge can be constructed by combination of a cross linking agent, or radiation of a high energy beam. The polyfunctional compound which generates bridge construction by a reaction with the carboxyl group which a hydrophilic copolymer has among these crosslinking methods can be used especially conveniently. As such a polyfunctional compound, a polyfunctional epoxy compound, polyvalent metal ion, chelate compound, etc. can be mentioned, for example. A hydroxyl content copolymer can be prepared and polyhydric alcohol can also be made to impregnate after bridge construction using a polyfunctional isocyanate compound. In the gel preparation constituent of this invention, a percutaneous absorption

auxiliary agent can be added if needed. As such a percutaneous absorption auxiliary agent, for example Limonene, menthol, Ethanol, isopropyl alcohol, butanol, lauryl alcohol, Benzyl alcohol, oleic acid, salicylic acid, and stearic acid–n–butyl, Myristic acid isopropyl, pulmitic acid isopropyl, diethyl sebacate, N,N–diethyl– m–torr amide, N–methyl pyrrolidone, N–ethylpyrrolidone, hyaluronic acid, crotamiton, etc. can be mentioned. An antiseptic, an antioxidant, a pH adjuster, an inorganic bulking agent, etc. can be added if needed. The gel preparation of this invention makes the layer which consists of a gel preparation constituent form on a support base. As construction material of a support base, the composite base material which pasted the porous base material together can be conveniently used for the base material which has barrier property to polyhydric alcohol and a pharmacological activity substance. By pasting a porous base material together to a barrier property base material, a tangle in a hydrophilic copolymer and a porous base material arises, and exfoliation of the layer which consists of a gel preparation constituent can be prevented. Pasting with a barrier property base material and a porous base material can be performed using adhesives or a binder, or heat sealing etc. can perform. As a barrier property base material, a sheet, a film, a synthetic paper which consist of synthetic resins, such as polyester, polyvinyl chloride, polyethylene, and polypropylene, can be used, for example. On the other hand, as a porous base material, a nonwoven fabric, textile fabrics, knitted fabric, etc. can be used, for example.

[0008]There is no restriction in particular in the method of manufacturing the gel preparation of this invention, and For example, a hydrophilic copolymer solution, A pharmacological activity substance and a cross linking agent are mixed, after applying and drying and making a bridge construct by heat–treatment on a support base, polyhydric alcohol can be applied further and the layer which consists of a gel preparation constituent at two processes can be formed. Or a hydrophilic copolymer solution, polyhydric alcohol, a pharmacological activity substance, and a cross linking agent are mixed, on a support base, it can apply and dry and the layer which constructs a bridge by heat–treatment and consists of a gel preparation constituent at one process can be formed. The gel preparation of this invention can paste the film for exfoliation together on the surface if needed. The polyester film etc. which restriction in particular does not have in the film for exfoliation to be used, for example, carried out one side exfoliation processing can be used conveniently. When the film for exfoliation is pasted together, peel–off and the gel side of gel preparation are stuck for the film for exfoliation on the skin in the case of use. A pharmacological activity substance is endermically absorbed by urgency by excelling and sticking the gel preparation of this invention on percutaneous absorption. Drawing 1 is a sectional view of one mode of the gel preparation of this invention. On the support base by which the porous base material 3 was stuck on the barrier property base material 1 via the adhesive layer 2, the layer 4 which consists of a gel preparation constituent is formed, and the film 5 for exfoliation is further pasted together on it.

[0009]

[Working example]Although an embodiment is given to below and this invention is explained to it still in detail, this invention is not limited at all by these embodiments.

The example 1 (polymerization of a hydrophilic copolymer) of preparation

48 g of methyl acrylate, 30 g of ethyl acrylate, the acrylic acid 20g, and 2 g of acrylic acid–2–hydroxyethyl, It dissolved in the ethyl acetate 93g and a mixed solvent with 93 g of methyl ethyl ketone, and further, after adding 0.57 g of 2,2'–azobisisobutyronitrile, the polymerization was performed at 55 ** under a nitrogen atmosphere for 24 hours, and the hydrophilic copolymer solution A was prepared.

The example 2 (polymerization of a hydrophilic copolymer) of preparation

The hydrophilic copolymer solution B was prepared by the same method as the example 1 of preparation using 42.5 g of methyl acrylate, 42.5g of ethyl acrylate, and the acrylic acid 15g.

The example 3 (polymerization of a hydrophilic copolymer) of preparation

0.3 g of benzoyl peroxide was added to the mixed solution of the acrylic acid 50g, 10 g of maleic anhydrides, 20 g of methyl acrylate, 20 g of ethyl acrylate, and the methanol 250g, the polymerization was performed at 70 ** under a nitrogen atmosphere for 10 hours, and the hydrophilic copolymer solution C was obtained.

The example 4 (polymerization of a hydrophilic copolymer) of preparation
Added the potassium persulfate 0.02g to the mixed solution of the acrylic acid 80g, 20 g of methyl acrylate, and the water 50g as a polymerization initiator, it was made to trickle continuously into the reaction vessel into which the water 150g was put, and it was made to react to it at 85 ** for 5 hours. The polymerization was advanced at 85 ** after the end of dropping for 3 hours, and the hydrophilic copolymer solution D was obtained.
The example 5 (preparation of a hydrophilic copolymer) of preparation
Vinyl methyl ether maleic anhydride copolymer [VEMA-A106, the Daicel Chemical Industries, Ltd. make, ] with 37.2 weight % of vinylmethyl ether and a maleic anhydride of 62.8 weight % 20 g was distributed in the ethanol 80g, several drops of chlorides were added, a reaction was performed at 70 ** for about 6 hours, and the hydrophilic copolymer solution E was obtained.
The example 6 (preparation of a hydrophilic copolymer) of preparation
Vinyl methyl ether maleic anhydride copolymer [VEMA-A106, the Daicel Chemical Industries, Ltd. make, ] with 37.2 weight % of vinylmethyl ether and a maleic anhydride of 62.8 weight % 20 g was distributed in the methanol 80g, several drops of chlorides were added, a reaction was performed at 70 ** for about 6 hours, and the hydrophilic copolymer solution F was obtained.
The example 7 (preparation of a hydrophilic copolymer) of preparation
Vinyl methyl ether maleic anhydride copolymer [VEMA-A106, the Daicel Chemical Industries, Ltd. make, ] with 37.2 weight % of vinylmethyl ether and a maleic anhydride of 62.8 weight % 20 g was distributed in the water 80g, several drops of chlorides were added, a reaction was performed at 70 ** for about 10 hours, and the hydrophilic copolymer solution G was obtained.
The example 8 (preparation of a hydrophilic copolymer) of preparation
Styrene maleic anhydride copolymer [SMA-1000A, Elf Atochem North America, a product made from Inc., ] with 51.5 weight % of styrene and a maleic anhydride of 48.5 weight % 20 g was distributed in the ethanol 80g, several drops of phosphoric acid was added, a reaction was performed at 70 ** for about 10 hours, and the hydrophilic copolymer solution H was obtained.
The example 9 (preparation of a hydrophilic copolymer) of preparation
Styrene maleic anhydride copolymer [SMA-1000A, Elf Atochem North America, the product made from Inc., ] with 51.5 weight % of styrene and a maleic anhydride of 48.5 weight % 20 g was distributed in the water 80g, several drops of phosphoric acid was added, the reaction was performed at 90 ** for about 8 hours, and the hydrophilic copolymer solution I was obtained.
The example 10 (production of a support base) of preparation
After having applied, drying and making a bridge construct on 16-micrometer-thick polyester film so that the thickness after drying an acrylic-pressure-sensitive-adhesive solution may be set to 5 micrometers, the nonwoven fabric of basis weight 30 $g/m^2$ was laminated, and the support base was produced.
To the embodiment 1 hydrophilic-nature copolymer solution A100g, 17.5g of progesterone, and the polyfunctional isocyanate [coronate L. ] made from Japanese Polyurethane 0.1 g is added, and it applied and dried and the bridge was made to construct over the nonwoven fabric face of the support base which produced this in the example 10 of preparation so that the coverage after desiccation may become 50 $g/m^2$. Next, Mai Ya Bar was used for the coating surface acquired by doing in this way, propylene glycol was applied so that coverage might become 50 $g/m^2$, polyester film with a thickness of 38 micrometers which carried out one side exfoliation processing on this further was pasted together, and gel preparation was produced.
Instead of progesterone in embodiment 2 Embodiment 1, gel preparation was produced by the completely same operation as Embodiment 1 except having used nifedipine as a pharmacological activity substance.Instead of progesterone in embodiment 3 Embodiment 1, testosterone was used as a pharmacological activity substance and gel preparation was produced by the completely same operation as Embodiment 1 instead of polyfunctional isocyanate except having used [E-AX and Soken Chemical & Engineering make] made from polyfunctional epoxy cross-linking agent 1.0g.
Instead of the propylene glycol in embodiment 4 Embodiment 1, gel preparation was produced by the completely same operation as Embodiment 1 except having used the polypropylene glycol

(molecular weight 400) as polyhydric alcohol.
To the embodiment 5 hydrophilic-nature copolymer solution B100g, 17.5 g of pindolol, The propylene glycol 105g and [E-AX and Soken Chemical & Engineering make] made from polyfunctional epoxy cross-linking agent 2.0g were added, and the bridge was made to apply, dry and construct so that the coverage after drying to the nonwoven fabric face of the support base which produced this in the example 10 of preparation may become 75 g/$m^2$. Polyester film with a thickness of 38 micrometers which carried out one side exfoliation processing was pasted together on this, and gel preparation was produced.
Instead of the propylene glycol in embodiment 6 Embodiment 5, gel preparation was produced by the completely same operation as Embodiment 5 except having used the polyethylene glycol (molecular weight 400 [ about ]) as polyhydric alcohol.
Gel preparation was produced by the completely same operation as Embodiment 1 except the addition of progesterone in embodiment 7 Embodiment 1 having been 5.0 g instead of 17.5 g.
Gel preparation was produced by the completely same operation as Embodiment 1 except the addition of progesterone in embodiment 8 Embodiment 1 having been 24.5 g instead of 17.5 g.
To the embodiment 9 hydrophilic-nature copolymer solution C100g, 30 g of clonidine, the propylene glycol 100g, 5 g of myristic acid isopropyl and the ethylene glycol diglycidyl ether 0.1g were added, and the bridge was made to apply, dry and construct so that the coverage after drying to the nonwoven fabric face of the support base which produced this in the example 10 of preparation may become 50 g/$m^2$. Polyester film with a thickness of 38 micrometers which carried out one side exfoliation processing was pasted together on this, and gel preparation was produced.
Instead of the hydrophilic copolymer solution C in embodiment 10 Embodiment 9, the hydrophilic copolymer solution D was used and gel preparation was produced by the completely same operation as Embodiment 9 instead of clonidine except having used lidocaine as a pharmacological activity substance.
Instead of the hydrophilic copolymer solution C in embodiment 11 Embodiment 9, the hydrophilic copolymer solution E was used and gel preparation was produced by the completely same operation as Embodiment 9 instead of clonidine except having used estradiol as a pharmacological activity substance.
To the embodiment 12 hydrophilic-nature copolymer solution E100g, 10g of testosterone, and polyfunctional epoxy cross-linking agent [E-AX, Soken Chemical & Engineering] 0.5 g is added, and it applied and dried and the bridge was made to construct over the nonwoven fabric face of the support base which produced this in the example 10 of preparation so that the coverage after desiccation may become 50g[/m ] $^2$. Next, Mai Ya Bar was used for the coating surface acquired by doing in this way, propylene glycol was applied so that coverage might become 50 g/$m^2$, polyester film with a thickness of 38 micrometers which carried out one side exfoliation processing on this further was pasted together, and gel preparation was produced.
Instead of the hydrophilic copolymer solution E in embodiment 13 Embodiment 12, gel preparation was produced by the completely same operation as Embodiment 12 except having used the hydrophilic copolymer solution F.
Instead of the hydrophilic copolymer solution E in embodiment 14 Embodiment 12, gel preparation was produced by the completely same operation as Embodiment 12 except having used the hydrophilic copolymer solution G.
Instead of the hydrophilic copolymer solution E in embodiment 15 Embodiment 12, gel preparation was produced by the completely same operation as Embodiment 12 except having used the hydrophilic copolymer solution H.
Instead of the hydrophilic copolymer solution E in embodiment 16 Embodiment 12, gel preparation was produced by the completely same operation as Embodiment 12 except having used the hydrophilic copolymer solution I.
To the comparative example 1 hydrophilic-nature copolymer solution A100g, 17.5g of progesterone, and the polyfunctional isocyanate [coronate L. ] made from Japanese Polyurethane 0.1 g is added, and it applied and dried and the bridge was made to construct over

a nonwoven fabric face of a support base which produced this in the example 10 of preparation so that coverage after desiccation may become 50 g/$m^2$. Next, polyester film with a thickness of 38 micrometers which carried out one side exfoliation processing was pasted together on this, and matrix type pharmaceutical preparation was produced.
Instead of progesterone in the comparative example 2 comparative example 1, matrix type pharmaceutical preparation was produced by the completely same operation as the comparative example 1 except having used nifedipine as a pharmacological activity substance.
Instead of progesterone in the comparative example 3 comparative example 1, testosterone is used as a pharmacological activity substance, Instead of polyfunctional isocyanate, matrix type pharmaceutical preparation was produced by the completely same operation as the comparative example 1 except having used [E-AX and Soken Chemical & Engineering make] made from polyfunctional epoxy cross-linking agent 1.0g.
Instead of the hydrophilic copolymer solution A in the comparative example 4 comparative example 3, the hydrophilic copolymer solution B was used and matrix type pharmaceutical preparation was produced by the completely same operation as the comparative example 3 instead of testosterone except having used pindolol as a pharmacological activity substance.
To a comparative example 5 acrylic emulsion (loam & hearth company make, primal N-580, 50 weight % of solid content). It blended 18.3weight % by having made clonidine into solid content, and the bridge was made to apply, dry and construct so that coverage after drying to a nonwoven fabric face of a support base which produced this in the example 10 of preparation may become 50 g/$m^2$. Polyester film with a thickness of 38 micrometers which carried out one side exfoliation processing was pasted together on this, and matrix type pharmaceutical preparation was produced.
Matrix type pharmaceutical preparation was produced by the completely same operation as the comparative example 5 except having made lidocaine into solid content and having blended it 17.8weight % as a pharmacological activity substance, instead of clonidine of the comparative example 6 comparative example 5.
Matrix type pharmaceutical preparation was produced by the completely same operation as the comparative example 5 except having made estradiol into solid content and having blended it 19.4weight % as a pharmacological activity substance, instead of clonidine of the comparative example 7 comparative example 5.To 100 g of comparative example 8 acrylic emulsions (loam & hearth company make, primal N-580, 50 weight % of solid content). 25 g of progesterone, the propylene glycol 105g, and polyfunctional epoxy cross-linking agent [E-AX, Soken Chemical & Engineering] 2.0 g was added, to a nonwoven fabric face of a support base which produced this in the example 10 of preparation, it applied and dried so that coverage after desiccation might become 50 g/$m^2$, and polyester film with a thickness of 38 micrometers which carried out one side exfoliation processing on this was pasted together, and matrix type pharmaceutical preparation was produced.
To the comparative example 9 hydrophilic-nature copolymer solution E100g, 10g of testosterone, and polyfunctional epoxy cross-linking agent [E-AX, Soken Chemical & Engineering] 0.5 g is added, and it applied and dried and the bridge was made to construct over a nonwoven fabric face of a support base which produced this in the example 10 of preparation so that coverage after desiccation may become 50g[/m ] $^2$. Polyester film with a thickness of 38 micrometers which carried out one side exfoliation processing was pasted together on this, and matrix type pharmaceutical preparation was produced.
Instead of the hydrophilic copolymer solution E in the comparative example 10 comparative example 9, matrix type pharmaceutical preparation was produced by the completely same operation as the comparative example 9 except having used the hydrophilic copolymer solution F.Instead of the hydrophilic copolymer solution E in the comparative example 11 comparative example 9, matrix type pharmaceutical preparation was produced by the completely same operation as the comparative example 9 except having used the hydrophilic copolymer solution G.Instead of the hydrophilic copolymer solution E in the comparative example 12 comparative example 9, matrix type pharmaceutical preparation was produced by the completely same

operation as the comparative example 9 except having used the hydrophilic copolymer solution H.Instead of the hydrophilic copolymer solution E in the comparative example 13 comparative example 9, matrix type pharmaceutical preparation was produced by the completely same operation as the comparative example 9 except having used the hydrophilic copolymer solution I.A skin radiographic examination of a pharmacological activity substance of pharmaceutical preparation was done by a following method. Drawing 2 is a sectional view of equipment used for a skin radiographic examination of a pharmacological activity substance. In the thermostat 6 which kept water temperature at 37 **, the length type Francis type cell 7 is installed. A cell is equipped with the abdomen extraction skin 8 depilated as a transmission film with an animal clipper of the with a weights [ 150-170g ] Wister system rat (male), and the pharmaceutical preparation 9 is stuck on the skin. A transmission surface product is 1.76 $cm^2$. Penetration side 10 is filled up with a phosphoric acid buffer solution of pH 7.2, and it agitates by the rotator 12 using the stirrer 11. Liquid is temporally sampled from the sampling port 13, the abdomen extraction skin 8 of a rat is penetrated from the pharmaceutical preparation 9 by HPLC (high performance chromatography), and concentration of a pharmacological activity substance which dissolved in buffer solution is quantified. Measurement computes accumulation transmission quantity of a pharmacological activity substance from the average value repeatedly using the skin of ten Wister system rats 10 times.
The pharmaceutical preparation of Embodiment 1, Embodiment 4, Embodiment 7, Embodiment 8, and the comparative example 1 which blended progesterone as an example of evaluation 1 pharmacological-activity substance was evaluated. The accumulation transmission quantity of progesterone of the gel preparation of Embodiment 1, After [ 1.5 hours ] 0.0microg/$cm^2$, after [ 3.5 hours ] 0.4microg/$cm^2$, They were after [ 6 hours ] 1.8microg/$cm^2$, after [ 17.5 hours ] 11.2microg/$cm^2$, after [ 19.5 hours ] 12.6microg/$cm^2$, after [ 21.5 hours ] 14.0microg/$cm^2$, and after [ 23.5 hours ] 15.1microg/$cm^2$. The accumulation transmission quantity of progesterone of the gel preparation of Embodiment 4, After [ 1.5 hours ] 0.4microg/$cm^2$, after [ 3.5 hours ] 1.4microg/$cm^2$, They were after [ 6 hours ] 3.9microg/$cm^2$, after [ 17.5 hours ] 18.6microg/$cm^2$, after [ 19.5 hours ] 21.4microg/$cm^2$, after [ 21.5 hours ] 23.2microg/$cm^2$, and after [ 23.5 hours ] 24.9microg/$cm^2$. The accumulation transmission quantity of progesterone of the gel preparation of Embodiment 7, After [ 1.5 hours ] 0.1microg/$cm^2$, after [ 3.5 hours ] 0.3microg/$cm^2$, They were after [ 6 hours ] 0.9microg/$cm^2$, after [ 17.5 hours ] 4.2microg/$cm^2$, after [ 19.5 hours ] 4.9microg/$cm^2$, after [ 21.5 hours ] 5.8microg/$cm^2$, and after [ 23.5 hours ] 6.9microg/$cm^2$. The accumulation transmission quantity of progesterone of the gel preparation of Embodiment 8, After [ 1.5 hours ] 0.2microg/$cm^2$, after [ 3.5 hours ] 1.0microg/$cm^2$, They were after [ 6 hours ] 3.1microg/$cm^2$, after [ 17.5 hours ] 17.1microg/$cm^2$, after [ 19.5 hours ] 20.0microg/$cm^2$, after [ 21.5 hours ] 22.6microg/$cm^2$, and after [ 23.5 hours ] 23.9microg/$cm^2$. The accumulation transmission quantity of progesterone of the matrix type pharmaceutical preparation of the comparative example 1, After [ 1.5 hours ] 0.0microg/$cm^2$, after [ 3.5 hours ] 0.0microg/$cm^2$, They were after [ 6 hours ] 0.0microg/$cm^2$, after [ 17.5 hours ] 2.8microg/$cm^2$, after [ 19.5 hours ] 4.2microg/$cm^2$, after [ 21.5 hours ] 6.0microg/$cm^2$, and after [ 23.5 hours ] 7.4microg/$cm^2$. The change with time of the accumulation transmission quantity of progesterone is shown in drawing 3. As seen in this figure, the gel preparation using this invention constituent containing polyhydric alcohol of Embodiment 1 and Embodiment 4 excels the matrix type pharmaceutical preparation of the comparative example 1 using the constituent which does not contain polyhydric alcohol in the skin permeability of progesterone. Each used propylene glycol as polyhydric alcohol, and if the accumulation transmission quantity of progesterone of the matrix formulation of Embodiment 1, Embodiment 7, and Embodiment 8 from which the addition of progesterone differs is measured, accumulation transmission quantity has increased as what has many additions of progesterone. Although the addition of progesterone of the gel preparation of Embodiment 7 is about 28.5% of an addition of progesterone of the matrix type pharmaceutical

preparation of the comparative example 1, it turns out that the gel preparation of Embodiment 7 shows the accumulation transmission quantity of progesterone almost comparable as the matrix type pharmaceutical preparation of the comparative example 1.
The pharmaceutical preparation of Embodiment 2 and the comparative example 2 which blended nifedipine as an example of evaluation 2 pharmacological-activity substance was evaluated. The gel preparation of Embodiment 2 of the accumulation transmission quantity of nifedipine of 23.5 hours after is 55.1microg/$cm^2$.
The matrix type pharmaceutical preparation of the comparative example 2 was 10.1microg/$cm^2$.
The change with time of the accumulation transmission quantity of nifedipine is shown in drawing 4. From this result, the matrix type pharmaceutical preparation of the comparative example 2 using the constituent in which the gel preparation using this invention constituent of Embodiment 2 containing polyhydric alcohol does not contain polyhydric alcohol shows excelling in the skin permeability of nifedipine.
The pharmaceutical preparation of Embodiment 3 and the comparative example 3 which blended testosterone as an example of evaluation 3 pharmacological-activity substance was evaluated. The gel preparation of Embodiment 3 of the accumulation transmission quantity of testosterone of 23.5 hours after is 81.9microg/$cm^2$.
The matrix type pharmaceutical preparation of the comparative example 3 was 6.3microg/$cm^2$.
The change with time of the accumulation transmission quantity of testosterone is shown in drawing 5. From this result, the matrix type pharmaceutical preparation of the comparative example 3 using the constituent in which the gel preparation using this invention constituent of Embodiment 3 containing polyhydric alcohol does not contain polyhydric alcohol shows excelling in the skin permeability of testosterone.
The pharmaceutical preparation of Embodiment 5, Embodiment 6, and the comparative example 4 which blended pindolol as an example of evaluation 4 pharmacological-activity substance was evaluated. The gel preparation of Embodiment 5 of the accumulation transmission quantity of pindolol of 23.5 hours after is 220microg/$cm^2$.
The gel preparation of Embodiment 6 was 117microg/$cm^2$, and the matrix formulation of the comparative example 4 was 27microg/$cm^2$.
The change with time of the accumulation transmission quantity of pindolol is shown in drawing 6. From this result, the matrix type pharmaceutical preparation of the comparative example 4 using the constituent in which the gel preparation using this invention constituent containing polyhydric alcohol of Embodiment 5 and Embodiment 6 does not contain polyhydric alcohol shows excelling in the skin permeability of pindolol. The result of evaluation is collectively shown in the 1st table.
[0010]
[Table 1]

第1表

| | 薬理活性物質 | 添加量（g） | 23.5時間後の累積透過量（μg／cm²） |
|---|---|---|---|
| 実施例1 | プロゲステロン | 17.5 | 15.1 |
| 実施例4 | プロゲステロン | 17.5 | 24.9 |
| 実施例7 | プロゲステロン | 5.0 | 6.9 |
| 実施例8 | プロゲステロン | 24.5 | 23.9 |
| 比較例1 | プロゲステロン | 17.5 | 7.4 |
| 実施例2 | ニフェジピン | 17.5 | 55.1 |
| 比較例2 | ニフェジピン | 17.5 | 10.1 |
| 実施例3 | テストステロン | 17.5 | 81.9 |
| 比較例3 | テストステロン | 17.5 | 6.3 |
| 実施例5 | ピンドロール | 17.5 | 220 |
| 実施例6 | ピンドロール | 17.5 | 117 |
| 比較例4 | ピンドロール | 17.5 | 27 |

[0011]As an example of evaluation 5 pharmacological-activity substance, the pharmaceutical preparation of Embodiments 9-11 and the comparative examples 5-8 which blended clonidine, lidocaine, estradiol, and progesterone was evaluated. The accumulation transmission quantity of the pharmacological activity substance 24 hours after application, In the clonidine of the gel preparation of Embodiment 9, the lidocaine of the gel preparation of 625microg/$cm^2$ and Embodiment 10 2,920microg/$cm^2$, In the estradiol of the gel preparation of Embodiment 11, the clonidine of 1.2microg/$cm^2$ and the matrix type pharmaceutical preparation of the comparative example 5 was [ the lidocaine of 160microg/$cm^2$ and the matrix type pharmaceutical preparation of the comparative example 6 ] 1,350microg/$cm^2$. Estradiol was not detected about the matrix type pharmaceutical preparation of the comparative example 7. Since propylene glycol carried out bleeding to the binder surface and adhesiveness was spoiled, the matrix type pharmaceutical preparation of the comparative example 8 did not evaluate. The result of evaluation is collectively shown in the 2nd table.

[0012]

[Table 2]

第2表

| | 薬理活性物質 | 24時間後の累積透過量（μg／cm²） |
|---|---|---|
| 実施例9 | クロニジン | 625 |
| 比較例5 | クロニジン | 160 |
| 実施例10 | リドカイン | 2920 |
| 比較例6 | リドカイン | 1350 |
| 実施例11 | エストラジオール | 1.2 |
| 比較例7 | エストラジオール | 検出されず |

[0013]The gel preparation of Embodiments 9-11 produced from the constituent which contains the hydrophilic copolymer solution C which consists of 60 weight % of monomeric units which have a carboxyl group, and 40 weight % of other copolymerizable vinyl system monomeric units, and propylene glycol from the result of the 2nd table, It turns out that it excels in the skin permeability of a pharmacological activity substance compared with the matrix type

pharmaceutical preparation of the comparative examples 5–7 produced from the constituent which contains an acrylic emulsion without the monomeric unit which has a carboxyl group, and does not contain polyhydric alcohol. The pharmaceutical preparation of the comparative example 8 produced from the constituent in which the monomeric unit which has a carboxyl group contains the acrylic emulsion and propylene glycol which are less than 10weight % of oleophilic copolymers, Since propylene glycol carried out bleeding to the binder surface, it turns out that it is required to make this hydrophilic copolymer construct a bridge in order to produce stable gel preparation using the hydrophilic copolymer which has a monomeric unit which has a carboxyl group.

As an example of evaluation 6 pharmacological–activity substance, the pharmaceutical preparation of Embodiments 12–16 and the comparative examples 9–13 which blended testosterone was evaluated. The accumulation transmission quantity of the pharmacological activity substance 24 hours after application, In Embodiment 12, 67.5microg/$cm^2$ and Embodiment 13 71.3microg/$cm^2$, In Embodiment 14, 49.6microg/$cm^2$ and Embodiment 15 56.8microg/$cm^2$, In 9.2microg/$cm^2$ and the comparative example 11, 4.1microg/$cm^2$ and the comparative example 12 were [ Embodiment 16 / 42.4microg/$cm^2$ and the comparative example 9 / 7.8microg/$cm^2$ and the comparative example 10 / 6.7microg/$cm^2$ and the comparative example 13 ] 5.4microg/$cm^2$. The result of evaluation is collectively shown in the 3rd table.

[0014]

[Table 3]

第３表

| | 親水性共重合体 | 多価アルコール | ２４時間後の累積透過量（μｇ／cm²） |
|---|---|---|---|
| 実施例１２ | E | プロピレングリコール | ６７．５ |
| 比較例９ | E | なし | ７．８ |
| 実施例１３ | F | プロピレングリコール | ７１．３ |
| 比較例１０ | F | なし | ９．２ |
| 実施例１４ | G | プロピレングリコール | ４９．６ |
| 比較例１１ | G | なし | ４．１ |
| 実施例１５ | H | プロピレングリコール | ５６．８ |
| 比較例１２ | H | なし | ６．７ |
| 実施例１６ | I | プロピレングリコール | ４２．４ |
| 比較例１３ | I | なし | ５．４ |

[0015]From the result of the 3rd table, the matrix formulation of the comparative examples 9–13 using the constituent in which the gel preparation of Embodiments 12–16 which contain propylene glycol as polyhydric alcohol does not contain polyhydric alcohol shows excelling in the skin permeability of testosterone.

[0016]

[Effect of the Invention]By blending a lot of polyhydric alcohol, the gel preparation constituent and gel preparation of this invention raise the activity of the pharmacological activity substance in a base material, can enlarge a diffusion rate, can raise the skin transmission rate of a pharmacological activity substance, and can improve percutaneous absorption.

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[Translation done.]

* NOTICES *

## DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]
[Drawing 1]Drawing 1 is a sectional view of one mode of the gel preparation of this invention.
[Drawing 2]Drawing 2 is a sectional view of the equipment used for the skin radiographic examination of the pharmacological activity substance.
[Drawing 3]Drawing 3 is a graph which shows the change with time of the accumulation transmission quantity of progesterone.
[Drawing 4]Drawing 4 is a graph which shows the change with time of the accumulation transmission quantity of nifedipine.
[Drawing 5]Drawing 5 is a graph which shows the change with time of the accumulation transmission quantity of testosterone.
[Drawing 6]Drawing 6 is a graph which shows the change with time of the accumulation transmission quantity of pindolol.
[Explanations of letters or numerals]
1 Barrier property base material
2 Adhesive layer
3 Porous base material
4 The layer which consists of a gel preparation constituent
5 The film for exfoliation
6 Thermostat
7 Length type Francis type cell
8 The abdomen extraction skin of a rat
9 Pharmaceutical preparation
10 Penetration side
11 Stirrer
12 Rotator
13 Sampling port

[Translation done.]

* NOTICES *

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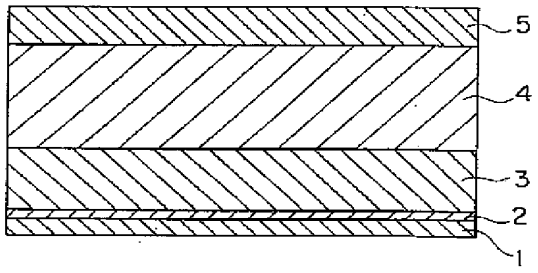
damages caused by the use of this translation.

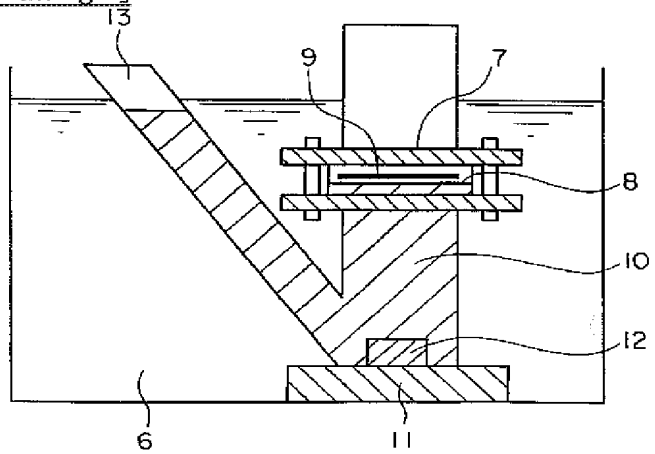
1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

## DRAWINGS

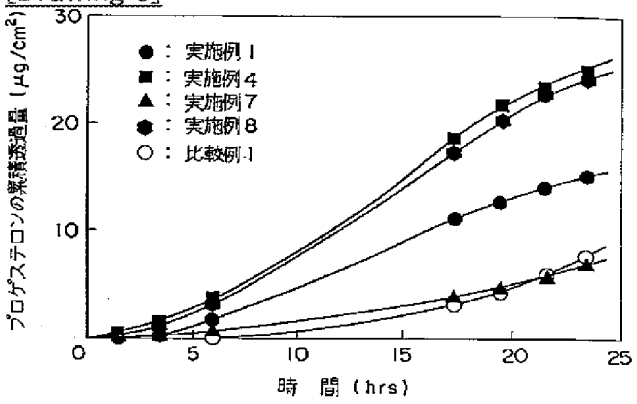
[Drawing 1]



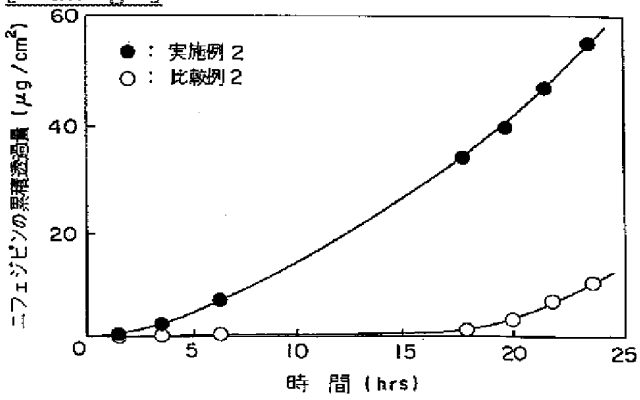

[Drawing 2]



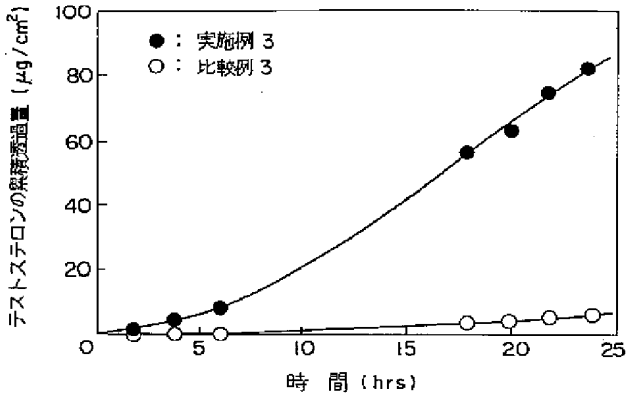

[Drawing 3]



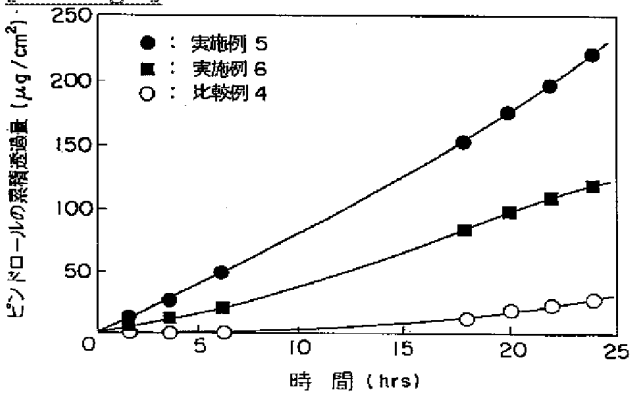

[Drawing 4]




[Drawing 5]




[Drawing 6]




[Translation done.]